Efficacy of Osimertinib Plus Bevacizumab vs Osimertinib in Patients With EGFR T790M–Mutated Non–Small Cell Lung Cancer Previously Treated With Epidermal Growth Factor Receptor–Tyrosine Kinase Inhibitor

West Japan Oncology Group 8715L Phase 2 Randomized Clinical Trial

Hiroaki Akamatsu, MD, PhD; Yukihiro Toi, MD; Hitotoshi Hayashi, MD, PhD; Daichi Fujiimoto, MD; Motoko Tachihara, MD, PhD; Naoki Furuya, MD, PhD; Sakiko Otani, MD, PhD; Junichi Shimizu, MD, PhD; Nobuyuki Katakami, MD, PhD; Koichi Azuma, MD, PhD; Naoko Miura, MD, PhD; Kazumi Nishino, MD, PhD; Satoshi Hara, MD; Satoshi Teraoka, MD; Satoshi Morita, PhD; Kazuhiko Nakagawa, MD, PhD; Nobuyuki Yamamoto, MD, PhD

IMPORTANCE
Although treatment with first-generation epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) plus antiangiogenic inhibitor has shown promising efficacies in patients with EGFR-mutated lung adenocarcinoma, recent single-arm studies have suggested that osimertinib plus antiangiogenic inhibitor might not work synergistically.

OBJECTIVE
To explore the efficacy and safety of osimertinib plus bevacizumab compared with osimertinib alone in patients with lung adenocarcinoma with EGFR T790M mutation.

DESIGN, SETTING, AND PARTICIPANTS
Patients with advanced lung adenocarcinoma that progressed with prior EGFR-TKI treatment (other than third-generation TKI) and acquired EGFR T790M mutation were enrolled. This study comprises a lead-in part with 6 patients and a subsequent phase 2 part. In phase 2, patients were randomized to osimertinib plus bevacizumab or osimertinib alone in a 1:1 ratio.

INTERVENTIONS
The combination arm received oral osimertinib (80 mg, every day) plus intravenous bevacizumab (15 mg/kg, every 3 weeks) until progression or unacceptable toxic effects. The control arm received osimertinib monotherapy.

MAIN OUTCOMES AND MEASURES
The primary end point was progression-free survival (PFS) assessed by investigators. Secondary end points consisted of overall response rate, time to treatment failure, overall survival, and safety.

RESULTS
From August 2017 through September 2018, a total of 87 patients were registered (6 in the lead-in part and 81 in the phase 2 part [intention-to-treat population]). Among those randomized, the median (range) age was 68 (41-82) years; 33 (41%) were male; 37 (46%) had an Eastern Cooperative Oncology Group performance status of 0; and 21 (26%) had brain metastasis. Although the overall response rate was better with osimertinib plus bevacizumab than osimertinib alone (68% vs 54%), median PFS was not longer with osimertinib plus bevacizumab (9.4 months vs 13.5 months; adjusted hazard ratio, 1.44; 90% CI, 1.00 to 2.08; *P* = .20). Median time to treatment failure was also shorter in the combination arm vs the osimertinib arm (8.4 months vs 11.2 months; *P* = .12). Median overall survival was not different in the combination arm vs osimertinib arm (not reached vs 22.1 months; *P* = .96). In the combination arm, common adverse events of grade 3 or higher were proteinuria (n = 9; 23%), hypertension (n = 8; 20%).

CONCLUSIONS AND RELEVANCE
In this randomized clinical trial comparing osimertinib plus bevacizumab vs osimertinib alone, the combination arm failed to show prolongation of PFS in patients with advanced lung adenocarcinoma with EGFR T790M mutation.

TRIAL REGISTRATION
UMIN Clinical Trials Registry Identifier: UMIN000023761

Published online January 7, 2021.
Among metastatic non–small cell lung cancer (NSCLC), EGFR mutation is the second most frequent genetic driver. First-generation and second-generation epithelial growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) have shown favorable efficacy over cytotoxic chemotherapy in patients with NSCLC with EGFR mutation.1-2 However, these patients ultimately experience disease progression within 10 to 13 months. Translational analyses revealed that about half of tumors acquired EGFR exon 20 T790M mutation as the most common mechanism of resistance.3

Osimertinib is an orally available covalent third-generation EGFR-TKI that has shown activity in both EGFR sensitizing (exon 19 deletion or exon 21 L858R) and exon 20 T790M mutations in a preclinical study.4 Among patients with NSCLC with EGFR T790M mutation, a phase 3 trial (AURA3)5 showed significant prolongation of progression-free survival (PFS) compared with platinum doublet chemotherapy. However, median PFS with osimertinib was again almost 10 months. Considering the tolerability of osimertinib monotherapy, a novel combination strategy to delay progression has been warranted.

Vascular endothelial growth factor (VEGF) plays a crucial role in cancer through its proliferation or metastasis, and several anti-VEGF inhibitors have already been developed. Bevacizumab is a humanized monoclonal IgG1 antibody that binds to VEGF and has shown clinical efficacy against various types of malignant neoplasms. In a preclinical study, EGFR-TKI plus anti-VEGF inhibitor showed synergistic effect in EGFR T790M xenograft model.6 Moreover, several prospective studies have shown preferable efficacy among patients with EGFR sensitizing7-8 and preexisting T790M variants.9 However, the efficacy and safety of osimertinib in combination with bevacizumab have not yet been elucidated. This study aims to test this combination in patients with EGFR-mutated NSCLC that progressed with prior EGFR-TKI treatment and acquired EGFR T790M mutation.

Methods

Study Design

This open-label, multi-institutional study comprises a lead-in part to assess the feasibility of combination treatment, followed by a randomized phase 2 part. In the lead-in part, 6 patients were treated with a fixed dose of osimertinib (80 mg/d) and bevacizumab (15 mg/kg, every 3 weeks). If more than 2 patients in this cohort experienced dose-limiting toxicity (DLT) in the first cycle, this study would be terminated. The definition of DLT was as follows: (1) nonhematologic toxic effect of grade 3 or greater, (2) hypertension of grade 4, or (3) interstitial lung disease of grade 2 or greater. After confirming the feasibility of this lead-in part, the phase 2 part was initiated, and eligible patients were equally randomized to the osimertinib arm or the combination arm. Randomization was stratified according to sex (male vs female), number of prior cytotoxic chemotherapy treatments (0 vs ≥1), and institution. The primary end point of the phase 2 part was PFS assessed by investigators. Secondary end points were overall response rate (ORR), time to treatment failure (TTF), overall survival (OS), and safety. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Ethical Considerations

The study was conducted in compliance with the principles of the Declaration of Helsinki,10 and the institutional review board of each participating institution approved the protocol. Written informed consent was obtained from all patients before any screening or inclusion procedures. The trial protocol is available in Supplement 1.

Eligibility and Exclusion Criteria

Eligible patients were (1) those with pathologically confirmed lung adenocarcinoma with EGFR sensitizing mutation, (2) those diagnosed as stage IIIb or IV in accordance with the seventh version of the American Joint Committee on Cancer staging criteria for lung cancer, or relapsed as metastatic disease after curative treatment, (3) those previously treated with the first-generation or second-generation EGFR-TKI and confirmed radiological progression, (4) those whose cancer was confirmed to acquire EGFR exon 20 T790M mutation after EGFR-TKI treatment, (5) those with Eastern Cooperative Oncology Group performance status of 0 or 1, (6) those with a measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1., (7) those with adequate organ function, and (8) those who provided written informed consent for inclusion in this study. Testing for EGFR mutation was done by local sites using polymerase chain reaction–based methods. Patients were excluded if they had (1) interstitial lung disease at the time of registration, (2) higher risk of bleeding or embolism, (3) uncontrolled hypertension, (4) leptomeningeal disease, or (5) positivity for hepatitis B virus antigen. Those who had brain metastasis were eligible for inclusion unless they were symptomatic at the time of registration. Patients who had a prior history of cytotoxic chemotherapy treatment were also eligible, and those who received radiotherapy to the brain were allowed after a 14-day interval after the last fraction of radiotherapy.

Study Treatment and Assessment Procedures

All patients were orally administered 80 mg of osimertinib every day. Patients who participated in the lead-in part or...
were allocated to the combination arm in the phase 2 part were intravenously administered 15 mg/kg of bevacizumab on day 1, every 3 weeks. Both drugs were continued until disease progression, but patients were allowed to continue the study treatment beyond radiological progression when it was considered to be clinically beneficial. Osimertinib treatment could be suspended due to toxic effects and resumed at 40 mg per day. Bevacizumab treatment could be suspended due to toxic effects but should be resumed at the same dose. Bevacizumab treatment was discontinued if patients experienced severe toxic effects (ie, gastrointestinal perforation [any grade], thromboembolism, pulmonary hemorrhage [grade ≥2] or other hemorrhages, allergic reaction, or cardiac toxic effects [grade ≥3]). Bevacizumab treatment was also to be discontinued if patients had not recovered within 42 days from a toxic effect requiring suspension (ie, serum creatinine >1.5 mg/dL, proteinuria greater than 2+ or hypertension [grade 4]). These patients were allowed to continue osimertinib treatment.

To assess the efficacy, computed tomography of the chest and upper abdomen was assessed every 6 weeks. Brain magnetic resonance imaging was assessed every 6 weeks if patients had detected brain metastasis at the time of study entry. Adverse events (AEs) were graded using the Common Terminology Criteria for Adverse Events, version 4.0.

Sample Size Calculation
Previous studies\(^7\)\(^8\) compared the efficacy of adding anti-VEGF inhibitor to the first-generation EGFR-TKIs and showed a hazard ratio (HR) of 0.44 to 0.54 in PFS compared with EGFR-TKI alone. We therefore assumed that osimertinib plus bevacizumab would lead to a PFS about 7.4 months longer than with osimertinib monotherapy, which corresponded to an HR of 0.55. Based on previous studies, 74 patients were required to ensure a statistical power of 0.80 at a 2-sided α error of 0.20. Considering a dropout rate of 8%, 80 patients were finally required.

Statistical Analysis
The PFS was estimated using Kaplan-Meier curves. Median PFS with 95% CI was reported for each treatment arm. The difference in PFS between the 2 treatment arms was examined at the significance level of 0.20 using a stratified log-rank test using the stratification factors (sex, number of prior cytotoxic chemotherapy treatments, and institution). A Cox regression model was used to estimate the adjusted HR stratified by sex (male/female) and history of cytotoxic chemotherapy treatment (yes/no) and its 80% and 95% CIs. All tests for the secondary end points were carried out at a 5% α level. The TTF and OS were analyzed in a similar way to PFS. For the ORR, the point estimates and the 95% CI with the Pearson-Clopper method were provided. Difference in the ORR was estimated using the \(\chi^2\) test. Characteristics of the 2 arms were compared using the \(\chi^2\) test or analysis of variance. Statistical analyses were conducted with JMP software, version 11 (SAS Institute) and GraphPad Prism, version 7.00 for Windows (GraphPad Software). A \( P \) value less than .05 was considered to be significant.

Results
The flowchart of the participants is shown in Figure 1. From August 2017 through September 2018, a total of 87 patients were registered (6 in the lead-in part and 81 in the phase 2 part [intention-to-treat population]). Of 81 patients registered in the phase 2 part, 41 were allocated to the osimertinib arm, and 40 were allocated to the combination arm. All received at least 1 dose of study treatment; they were therefore analyzed as a safety population. At the time of data cutoff, all patients in the lead-in part finished study treatment, while 26 patients were still receiving treatment in the phase 2 part. The median (range) follow-up time in the phase 2 part was 16.2 (2.8-24.0) months in the osimertinib arm and 16.0 (2.4-22.6) months in the combination arm.

Lead-in Part
Baseline characteristics of the 6 patients are shown in eTable 1 in Supplement 2. No DLT was observed during the first cycle, and AEs during the whole study period were mostly grade 1 or 2 (eTable 2 in Supplement 2). Grade 3 AEs were hypertension, decreased neutrophil count, rash, and anemia (2 cases each). One patient had interstitial lung disease on day 31 but finally improved on day 46. Regarding efficacy, there were 5 patients with partial responses and 1 patient with stable disease. The median PFS was 11.5 months (95% CI, 3.7 months to not reached; eFigure 1 in Supplement 2).

Phase 2 Part
Baseline characteristics of the 81 patients are summarized in the Table. The median (range) age was 68 (41-82) years; 33 (41%) were male; 4 (5%), 59 (73%), and 18 (22%) had a clinical stage
IIIB, IV, and recurrence, respectively; 37 patients (46%) had an Eastern Cooperative Oncology Group performance status of 0 or and 44 (54%) had a status of 1; and 21 patients (26%) had brain metastasis. A total of 17 patients (21%) had prior history of cytotoxic chemotherapy treatment and 12 (15%) had prior history of anti-VEGF therapy.

Although ORR was higher in the combination arm (71.8%; 95% CI, 50.9%-81.4%) than in the osimertinib arm (55.0%; 95% CI, 37.4%-69.3%; Figure 2), it did not contribute to prolongation of PFS (13.5 months in the osimertinib arm vs 9.4 months in the combination arm; adjusted HR, 1.44; 95% CI, 0.83-2.52, respectively; \( P = .20 \); Figure 3A). Any subset analysis did not show significant difference in PFS (eFigure 2 in Supplement 2). Of those, prior history of anti-VEGF inhibitor seemed to have a detrimental effect on the combination treatment. In the combination arm, patients who had any history of anti-VEGF therapy showed significantly shorter PFS than those who did not (4.6 months vs 9.4 months; \( P = .04 \)).

### Table. Patient Characteristics in Phase 2 Part

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Osimertinib</td>
<td>Osimertinib + bevacizumab</td>
</tr>
<tr>
<td>Age, median (range), y</td>
<td>70 (41-82)</td>
<td>68 (43-82)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>17 (41)</td>
<td>16 (40)</td>
</tr>
<tr>
<td>Female</td>
<td>24 (59)</td>
<td>24 (60)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>20 (49)</td>
<td>21 (53)</td>
</tr>
<tr>
<td>Smoker or former smoker</td>
<td>21 (51)</td>
<td>19 (48)</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>17 (42)</td>
<td>20 (50)</td>
</tr>
<tr>
<td>1</td>
<td>24 (58)</td>
<td>20 (50)</td>
</tr>
<tr>
<td>Clinical stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIB</td>
<td>2 (5)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>IV</td>
<td>26 (63)</td>
<td>33 (83)</td>
</tr>
<tr>
<td>Recurrence</td>
<td>13 (32)</td>
<td>5 (12)</td>
</tr>
<tr>
<td>Previous EGFR-TKI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st Generation</td>
<td>35</td>
<td>36</td>
</tr>
<tr>
<td>2nd Generation</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>No. of prior cytotoxic chemotherapy treatments</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>34 (83)</td>
<td>30 (75)</td>
</tr>
<tr>
<td>≥1</td>
<td>7 (17)</td>
<td>10 (25)</td>
</tr>
<tr>
<td>Types of EGFR mutation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exon 20 T790M</td>
<td>41 (100)</td>
<td>40 (100)</td>
</tr>
<tr>
<td>Exon 19del</td>
<td>28 (68)</td>
<td>22 (55)</td>
</tr>
<tr>
<td>Exon 21 L858R</td>
<td>13 (32)</td>
<td>18 (45)</td>
</tr>
<tr>
<td>Prior anti-VEGF inhibitor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4 (10)</td>
<td>8 (20)</td>
</tr>
<tr>
<td>No</td>
<td>36 (88)</td>
<td>31 (78)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Brain metastasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>9 (22)</td>
<td>12 (30)</td>
</tr>
<tr>
<td>No</td>
<td>32 (78)</td>
<td>28 (70)</td>
</tr>
<tr>
<td>Sites of detecting EGFR exon 20 T790M</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral blood</td>
<td>10 (24)</td>
<td>8 (20)</td>
</tr>
<tr>
<td>Lung</td>
<td>19 (46)</td>
<td>18 (45)</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>4 (10)</td>
<td>6 (15)</td>
</tr>
<tr>
<td>Liver</td>
<td>1 (2)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Mediastinal lymph node</td>
<td>4 (10)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Pleura</td>
<td>2 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>1 (2)</td>
<td>6 (15)</td>
</tr>
</tbody>
</table>

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.
Figure 2. Waterfall Plot of Each Arm Showing Best Percentage Change in Tumor Burden From Baseline

A. Treatment with osimertinib

B. Treatment with osimertinib plus bevacizumab

A, Complete response (n = 2), partial response (n = 21), stable disease (n = 17), and disease progression (n = 1). B, Complete response (n = 2), partial response (n = 25), stable disease (n = 11), disease progression (n = 1), not evaluable (n = 1).

Figure 3. Kaplan-Meier Curves of Progression-Free Survival

A. Progression-free survival

B. Subgroup analysis

A, Kaplan-Meier curves of progression-free survival in the osimertinib arm (n = 41) and combination arm (n = 40). B, Subgroup analysis according to any history of anti-vascular endothelial growth factor (VEGF) therapy.
vs 11.1 months; HR, 0.41; 95% CI, 0.13-1.27; \( P = .03 \); Figure 3B) while prior exposure of anti-VEGF therapy did not affect PFS in the osimertinib arm (15.1 months vs 13.7 months; HR, 1.19; 95% CI, 0.31-4.61; \( P = .85 \)). The TTF was also longer in the osimertinib arm than in the combination arm (11.2 months vs 8.4 months; adjusted HR, 1.54; 95% CI, 0.90-2.69; \( P = .12 \); Figure 4A). Finally, median OS was not different between the arms (22.1 months in osimertinib arm vs not reached in the combination arm; adjusted HR, 1.02; 95% CI, 0.43-2.44; \( P = .96 \); Figure 4B).

Adverse events are shown in eTable 3 in Supplement 2. Like those observed in the lead-in part, most AEs were generally mild (grade 1 or 2). Common AEs observed in the combination arm were proteinuria (grade 1-2, \( n = 22 \), 55%; and grade 3, \( n = 9 \), 23%) and hypertension (grade 1-2, \( n = 16 \), 40%; and grade \( \geq 3 \), \( n = 8 \), 20%). The rates of proteinuria (\( n = 31 \), 78%) and hypertension (\( n = 24 \), 60%) were significantly higher in the combination arm, while the incidence of anemia (\( n = 27 \), 66%) was significantly higher in the osimertinib arm. The number of hematologic toxic effects and skin-related AEs was not increased by adding bevacizumab. There was no serious bleeding or embolism in the combination arm. About 11% (9 patients) of the entire population experienced interstitial lung disease, but all were grade 1 or 2.

Treatment exposure is summarized in eTable 4 in Supplement 2. Twenty-seven patients (33%) experienced dose interruption with osimertinib, but the proportion was similar between the arms (13 in the osimertinib arm vs 14 in the combination arm). Of the 55 patients who discontinued study treatment, 37 were due to disease progression and 15 were due to toxic effects. In the combination arm, 11 patients (28%) discontinued bevacizumab due to AEs, and median (range) number of bevacizumab administrations was 7.5 (1-28). However, post-hoc analysis showed that discontinuation of bevacizumab due to AEs did not affect PFS in the combination arm (eFigure 3 in Supplement 2).

At the data cutoff time, 53 patients finished study treatment and about 45 of them (85%) received poststudy treatment (eTable 5 in Supplement 2). Common treatment regimens were platinum doublet chemotherapy (22 patients) and EGFR-TKI rechallenge (21 patients).

**Discussion**

To our knowledge, this is the first randomized clinical trial to explore the efficacy of adding anti-VEGF inhibitor to osimertinib. Although ORR was slightly better in the combination arm, we could not show advantages in PFS and OS. Previous reports have suggested that EGFR-TKI plus anti-VEGF inhibitor might be more beneficial in patients with brain metastasis\(^{11} \) or pleural effusion\(^{12} \); however, none of our subgroup analyses could identify its advantage.

In patients with advanced NSCLC with \( EGFR \) mutation, 1 randomized-phase 2 trial\(^ {13} \) and 2 phase 3 trials\(^ {7,8} \) showed benefits in PFS with erlotinib plus anti-VEGF inhibitor compared with erlotinib alone. On the other hand, a recent phase 2 randomized clinical trial\(^ {14} \) had negative results (median PFS, 17.9 months vs 13.5 months; HR, 0.81; \( P = .39 \)), and similar unfavorable results have been reported in single-arm trials\(^ {9,15} \) (median PFS, 13.2 months and 14.4 months, respectively). Regarding osimertinib, 2 single-arm studies reported the preliminary results of combining anti-VEGF inhibitors. Among 49 treatment-naive patients with \( EGFR \) sensitizing variants, osimertinib plus bevacizumab demonstrated an ORR of 80% and a median PFS of 18.4 months.\(^ {16} \) Another phase 2 study of osimertinib plus ramucirumab in 25 patients with \( EGFR \) T790M variant showed an ORR of 76% and median PFS of 11.0 months.\(^ {17} \) Considering the efficacy data of osimertinib monotherapy in pivotal trials (18.9 months among EGFR-TKI–naive patients and 10.1 months among patients with \( EGFR \) T790M–mutated disease),\(^ {5,18} \) these phase 2 results were not so intriguing. The present study provided more reliable evidence by adopting a randomized study design. Our control arm showed outstanding PFS (median, 13 months), but this was comparable with the Japanese subset of AURA3.\(^ {19} \)
The reason why every single study did not show advantages with osimertinib plus anti-VEGF inhibitor has not been fully discussed. Both Paz-Ares et al.\(^{22}\) and the present study enrolled patients who had progression despite prior EGFR-TKI treatment; it is therefore possible to speculate that exposure to prior treatment and tumor regrowth could confer microenvironmental changes of the tumor that lead to resistance to anti-VEGF agents. Another possible explanation indicated from the subset analysis is that prior exposure to anti-VEGF inhibitor may induce a different tumor environment that prevents synergy between osimertinib and bevacizumab. Based on prior evidence,\(^{18}\) we allowed inclusion of patients who had prior anti-VEGF inhibitor treatment. However, as shown in Figure 3B, prior exposure to anti-VEGF inhibitor had a detrimental effect in the combination arm. Nonetheless, the PFS among those without any history of anti-VEGF inhibitor in the combination arm was not superior to that in patients receiving osimertinib monotherapy. Indeed, these hypotheses may not be applicable to the result from the first-line trial by Yu et al.\(^{16}\) We did not prepare any collections of tissue or plasma samples before and after treatment, so we could not discuss any potential resistance mechanism with bevacizumab\(^{21,22}\) in the current study.

**Limitations**

Our trial has several limitations. First, owing to the small number of patients, this single study may not be conclusive. However, we think it is important that this randomized study clearly replicated the findings from previous single-arm studies. The data will draw attention to the development of osimertinib plus anti-VEGF inhibitors in any lines of treatment while several trial groups are conducting larger studies. Second, regarding toxic effects, our participants showed relatively higher incidence of proteinuria. Previously, Japanese patients with NSCLC were more likely to show a higher rate of proteinuria with anti-VEGF inhibitors. For example, the incidence of proteinuria with chemotherapy plus anti-VEGF inhibitor was much higher in Japanese studies (any grade, 26%-50%; grade 3-4, 4%) than in global studies (any grade, 4%; grade 3-4, 1%).\(^{20,23,24}\) and similar tendency was observed between Yu et al.\(^{16}\) and the current study. This racial difference could affect the feasibility of bevacizumab to some extent; however, post-hoc analysis (eFigure 3 in Supplement 2) denied its influence on PFS. Nevertheless, the current study provides meaningful information; adding anti-VEGF to osimertinib did not have the desired affect among patients with EGFR T790M–mutated disease.

The results may also have implications for the choice of first-line regimen in patients with EGFR variant. Recent studies reported comparable PFS data between osimertinib alone (18.9 months in the FLAURA trial\(^{19}\)) and erlotinib plus anti-VEGF inhibitors (16.9 months in the NEJ026 trial\(^{27}\) and 19.4 months in the RELAY trial\(^{18}\)). The current study’s data suggested that the prior exposure to anti-VEGF inhibitors clearly had detrimental effect on second-line osimertinib plus bevacizumab. More importantly, this combination itself is no longer effective in patients with EGFR T790M–mutated disease. Reflecting the results of the current trial, the efficacy of osimertinib plus anti-VEGF therapy should be explored as first-line treatment. Several randomized studies (ie, WJOG 9717L trial[UMIN000030206] and NCT04181060) are ongoing, and these results are anticipated with interest.

**Conclusions**

Compared with osimertinib monotherapy, osimertinib plus bevacizumab failed to show prolongation of PFS in patients with EGFR T790M–mutated advanced lung adenocarcinoma.

---

**ARTICLE INFORMATION**

**Accepted for Publication:** October 1, 2020.

**Published Online:** January 7, 2021.


**Open Access:** This is an open access article distributed under the terms of the CC-BY-NC-ND License. © 2021 Akamatsu H et al. JAMA Oncology.

**Author Affiliations:** Internal Medicine III, Wakayama Medical University, Wakayama, Japan (Akamatsu, Teraoka, Yamamoto); Department of Pulmonary Medicine, Sendai Kousei Hospital, Miyagi, Japan (Toi); Department of Medical Oncology, Faculty of Medicine, Kindai University, Osaka, Japan (Hayashi, Nakagawa); Department of Respiratory Medicine, Kobe City Medical Center General Hospital, Hyogo, Japan (Fujimoto); Division of Respiratory Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, Hyogo, Japan (Tachihara); Division of Respiratory Medicine, Department of Internal Medicine, St Marianna University School of Medicine, Kanagawa, Japan (Furuya); Department of Thoracic Oncology, Aichi Cancer Center Hospital, Aichi, Japan (Shimizu); Department of Medical Oncology, Department of Pulmonary Medicine, Chemotherapy Center and Division of Clinical Research, Takarazuka City Hospital, Hyogo, Japan (Katakami); Division of Respiriology, Neurology, and Rheumatology, Department of Internal Medicine, Kurume University School of Medicine, Fukuoka, Japan (Azuma); Department of Thoracic Oncology, National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan (Miura); Department of Thoracic Oncology, Osaka International Cancer Institute, Osaka, Japan (Nishino); Department of Respiratory Medicine, Itami City Hospital, Hyogo, Japan (Hara); Department of Biomedical Statistics and Bioinformatics, Kyoto University Graduate School of Medicine, Kyoto, Japan (Morita).

**Author Contributions:** Dr Akamatsu (principal investigator) had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Akamatsu, Furuya, Nishino, Morita, Nakagawa, Yamamoto. Acquisition, analysis, or interpretation of data: All authors.

**Drafting of the manuscript:** Akamatsu, Hayashi, Fujimoto, Furuya, Otani, Shimizu, Nishino, Hara, Morita, Yamamoto.

**Critical revision of the manuscript for important intellectual content:** Akamatsu, Toi, Tachihara, Furuya, Shimizu, Katakami, Azuma, Miura, Nishino, Teraoka, Nakagawa, Yamamoto.

**Statistical analysis:** Akamatsu, Katakami, Morita.

**Obtained funding:** Akamatsu.

**Administrative, technical, or material support:** Akamatsu, Hayashi, Fujimoto, Tachihara, Furuya, Otani, Shimizu, Hara, Yamamoto. Supervision: Nakagawa, Yamamoto.

**Conflict of Interest Disclosures:** Dr Akamatsu reported receiving grants and personal fees from Chugai Pharmaceutical and MSD KK and personal fees from AstraZeneca KK, Boehringer Ingelheim Japan Inc., Bristol Myers Squibb, Eli Lilly Japan KK, Novartis Pharma KK, Ono Pharmaceutical, and Taiho Pharmaceutical outside the submitted work. Dr Toi reported receiving personal fees from AstraZeneca, Bristol Myers Squibb, MSD, and Ono Pharmaceutical during the conduct of the study. Dr Hayashi reported receiving grants and personal fees from AstraZeneca KK and Chugai Pharmaceutical during the conduct of the study; and grants and personal fees from Boehringer Ingelheim Japan, Ono Pharmaceutical, and Bristol Myers Squibb and personal fees from Eli Lilly Japan KK, Kyorin Pharmaceutical, Merck Biopharma, MSD KK, Novartis Pharmaceuticals KK, Pfizer Japan Inc., Shanghai HailHe Biopharma, and Taiho Pharmaceutical outside the submitted work. Dr Fujimoto reported receiving grants and personal fees from Chugai Pharmaceutical, MSD KK, and Ono Pharmaceutical.

---

**Conflict of Interest Disclosures:** Dr Akamatsu reported receiving grants and personal fees from Chugai Pharmaceutical and MSD KK and personal fees from AstraZeneca KK, Boehringer Ingelheim Japan Inc., Bristol Myers Squibb, Eli Lilly Japan KK, Novartis Pharma KK, Ono Pharmaceutical, and Taiho Pharmaceutical outside the submitted work. Dr Toi reported receiving personal fees from AstraZeneca, Bristol Myers Squibb, MSD, and Ono Pharmaceutical during the conduct of the study. Dr Hayashi reported receiving grants and personal fees from AstraZeneca KK and Chugai Pharmaceutical during the conduct of the study; and grants and personal fees from Boehringer Ingelheim Japan, Ono Pharmaceutical, and Bristol Myers Squibb and personal fees from Eli Lilly Japan KK, Kyorin Pharmaceutical, Merck Biopharma, MSD KK, Novartis Pharmaceuticals KK, Pfizer Japan Inc., Shanghai HailHe Biopharma, and Taiho Pharmaceutical outside the submitted work. Dr Fujimoto reported receiving grants and personal fees from Chugai Pharmaceutical, MSD KK, and Ono Pharmaceutical.
Osimertinib Plus Bevacizumab vs Osimertinib in Advanced Lung Cancer Previously Treated With EGFR-TKI

Original Investigation Research

jamaoncology.com


Role of the Funder/Sponsor: AstraZeneca Japan.

This study was presented at the European Society for Medical Oncology Virtual Congress 2020; September 19-21, 2020.

Meeting Presentation: This study was presented at the European Society for Medical Oncology Virtual Congress 2020; September 19-21, 2020.

Data Sharing Statement: See Supplement 3.

Additional Contributions: We are grateful to data managers and other support staff of the West Japan Oncology Group Trial, especially Koji Takeda, MD, and Shinichiro Nakamura, MD, PhD. The present study was conducted with support from the West Japan Oncology Group and the Okayama Lung Cancer Study Group Trial 1001. We acknowledge proofreading and editing by Benjamin Phillips, BA, at the Clinical Study Support Center, Wakayama Medical University. These individuals did not receive compensation for their contributions.

REFERENCES


When the Signal From Phase 2 Research Should Be a Warning Sign

Howard (Jack) West, MD

The article by Akamatsu and colleagues1 in this issue of JAMA Oncology describes a phase 2 randomized clinical trial that tests the value of adding the vascular endothelial growth factor inhibitor bevacizumab to osimertinib in 81 Japanese patients with EGFR mutation–positive advanced non–small cell lung cancer (NSCLC) and T790M mutation–positive acquired resistance on a prior epidermal growth factor receptor (EGFR) inhibitor. In contrast with what many of us may have expected, the data revealed no hint of a favorable signal for progression-free survival (PFS) or overall survival (OS) with the combination.

Notably, osimertinib is commonly administered as first-line treatment for EGFR mutation–positive advanced NSCLC today, in the wake of the observed significant efficacy benefit, including in OS, with osimertinib over a first-generation EGFR inhibitor in previously untreated patients with EGFR–mutated disease in the FLAURA trial.2 One might therefore argue that the results seen by Akamatsu and colleagues3 in patients with EGFR T790M–mutated disease with acquired resistance to a prior EGFR inhibitor may not apply to osimertinib/bevacizumab administered in the first-line setting. However, these negative results are consistent with those observed in the single-arm phase 1/2 trial conducted by Yu and colleagues4 of osimertinib with bevacizumab in previously untreated patients with advanced EGFR mutation–positive NSCLC. The investigators for this US-based trial3 demonstrated a median PFS of only 18.4 months, numerically inferior to the median PFS of 18.9 months with osimertinib alone in the global FLAURA trial.5 Meanwhile, studies from Japan of erlotinib with or without bevacizumab as first-line treatment for EGFR mutation–positive NSCLC have demonstrated a significant improvement in PFS not accompanied by an improvement in OS, nor have we yet seen a prolonged OS with the combination of erlotinib and ramucirumab over erlotinib alone.

Taken together, the available data on the combination of a vascular endothelial growth factor inhibitor with an EGFR inhibitor have not demonstrated a survival benefit over an EGFR inhibitor alone, and the emerging data with osimertinib/bevacizumab are best characterized as disappointing. Regardless, a phase 3 randomized clinical trial of osimertinib with or without bevacizumab (ClinicalTrials.gov Identifier: NCT04181060) is being conducted through ECOG-ACRIN, propelled by a presumption of benefit rather than an assessment of the clinical data available.

Unfortunately, we all too frequently see our optimistic hopes based on impressive data from phase 2 trials dispelled when these approaches are battle tested in a larger, multicenter trial; it is almost unprecedented to see results of a phase 3 trial emerge as far superior to those of a preceding phase 2 trial. Phase 2 trials are conducted to identify which strategies demonstrate such clear promise that they merit being explored in phase 3 trials, which require vast investment, including the opportunity for patients to participate in research that has a meaningful probability of becoming a significant clinical advance. It is regrettable if we bypass the critical step of awaiting the signal from smaller clinical trials, particularly if that signal is a warning sign of likely futility.

Conflict of Interest Disclosures: Dr West reported receiving personal fees as a consultant and speaker from AstraZeneca and Genentech/Roche outside the submitted work.

Editor’s Note

The article by Akamatsu and colleagues1 in this issue of JAMA Oncology describes a phase 2 randomized clinical trial that tests the value of adding the vascular endothelial growth factor inhibitor bevacizumab to osimertinib in 81 Japanese patients with EGFR mutation–positive advanced non–small cell lung cancer (NSCLC) and T790M mutation–positive acquired resistance on a prior epidermal growth factor receptor (EGFR) inhibitor. In contrast with what many of us may have expected, the data revealed no hint of a favorable signal for progression-free survival (PFS) or overall survival (OS) with the combination.

Notably, osimertinib is commonly administered as first-line treatment for EGFR mutation–positive advanced NSCLC today, in the wake of the observed significant efficacy benefit, including in OS, with osimertinib over a first-generation EGFR inhibitor in previously untreated patients with EGFR–mutated disease in the FLAURA trial.2 One might therefore argue that the results seen by Akamatsu and colleagues3 in patients with EGFR T790M–mutated disease with acquired resistance to a prior EGFR inhibitor may not apply to osimertinib/bevacizumab administered in the first-line setting. However, these negative results are consistent with those observed in the single-arm phase 1/2 trial conducted by Yu and colleagues4 of osimertinib with bevacizumab in previously untreated patients with advanced EGFR mutation–positive NSCLC. The investigators for this US-based trial3 demonstrated a median PFS of only 18.4 months, numerically inferior to the median PFS of 18.9 months with osimertinib alone in the global FLAURA trial.5 Meanwhile, studies from Japan of erlotinib with or without bevacizumab as first-line treatment for EGFR mutation–positive NSCLC have demonstrated a significant improvement in PFS not accompanied by an improvement in OS, nor have we yet seen a prolonged OS with the combination of erlotinib and ramucirumab over erlotinib alone.

Taken together, the available data on the combination of a vascular endothelial growth factor inhibitor with an EGFR inhibitor have not demonstrated a survival benefit over an EGFR inhibitor alone, and the emerging data with osimertinib/bevacizumab are best characterized as disappointing. Regardless, a phase 3 randomized clinical trial of osimertinib with or without bevacizumab (ClinicalTrials.gov Identifier: NCT04181060) is being conducted through ECOG-ACRIN, propelled by a presumption of benefit rather than an assessment of the clinical data available.

Unfortunately, we all too frequently see our optimistic hopes based on impressive data from phase 2 trials dispelled when these approaches are battle tested in a larger, multicenter trial; it is almost unprecedented to see results of a phase 3 trial emerge as far superior to those of a preceding phase 2 trial. Phase 2 trials are conducted to identify which strategies demonstrate such clear promise that they merit being explored in phase 3 trials, which require vast investment, including the opportunity for patients to participate in research that has a meaningful probability of becoming a significant clinical advance. It is regrettable if we bypass the critical step of awaiting the signal from smaller clinical trials, particularly if that signal is a warning sign of likely futility.

Conflict of Interest Disclosures: Dr West reported receiving personal fees as a consultant and speaker from AstraZeneca and Genentech/Roche outside the submitted work.